REMARKS

Claims 32-34, 51 and 78-95 are pending in the application. Claims 51 and 78-95 are under examination. With this amendment, claim 51, 78, 83-84, 89-90 and 94 have been amended and claims 79-81, 88, 91-92 and 95 have been canceled without prejudice to applicants wishing to pursue these claims in their original form in a related application. Support for the claim amendments can be found throughout the specification including at, for example, previously presented claims 81, 87 and 95 or page 21, lines 4-6. Accordingly, the amendment does not raise an issue of new matter and entry thereof is respectfully requested. Applicant has reviewed the rejections set forth in the April 9, 2008, Office Action and respectfully traverses all grounds of rejections for the reasons that follow.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 51 and 94 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite allegedly because claim 51 recites "a gene which encodes a nucleic acid comprising SEQ ID NO:777" and claim 94 recites "a polynucleotide that hybridizes under highly stringent conditions to a nucleotide sequence comprising SEQ ID NO:777." The Office contends that the gene in claim 51 cannot encode a nucleic acid, and that the stringent conditions in claim 94 must be defined. Office Action, pages 3, line 8 - page 4, line 2.

Claim 51 has been amended to recite ". . . a gene which expresses a nucleic acid comprising SEQ ID NO:777, . . . ;" claim 94 has been amended to recite ". . . stringent conditions of 50-60° C, 5X SSC, overnight, followed by washing twice at 65° C for 20 minute with each of 2X, 0.5X and 0.2x SSC containing 0.1% SDS, . . .," thereby obviating the rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph

I. Rejection of claims 51 and 78-95 for Enablement

Claims 51 and 78-95 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Office alleges that "[t]he specification does not reasonably provide enablement for methods of diagnosing any and all cancers or for the detection

of a propensity towards cancer, comprising the active steps of differential detection of myosin I mRNA, myosin I protein, the detection of differential myosin I mRNA levels, detection of "evidence of differential expression" of myosin I. The basis for this rejection is that the teachings of the specification do not enable the intended use of the claimed methods for the diagnosis of any and all cancers, or for the diagnosis of specific cancers such as colon cancer, lung cancer, pancreatic cancer, ovarian cancer, stomach cancer, breast cancer or prostate cancer. Office Action, page 4.

The Office cites the seven factors of *In re Wands*, 858 F. 2d 731 (Fed. Cir. 1988) in conducting the enablement analysis, however, selectively addresses only a subset of these factors before concluding that undue experimentation is required to practice the full scope of the claimed invention. Office Action, pages 4-7. Applicants respectfully traverse the grounds of this rejection for the following reasons.

Enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. *In re Wands,* at 737 & 738. Factors to be considered in determining whether undue experimentation would be required to practice an invention included (1) the nature of the claimed invention, (2) the breadth of the claims, (3) the relative skill in the art, (4) the state of the prior art, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary to make or use the invention, (7) the amount of direction or guidance presented in the application, and (8) the predictability or unpredictability of the art. *Id.* No one factor is determinative, and the enablement requirement is met if a preponderance of the evidence indicates that it is more likely than not that any person skilled in the art at the time the application was filed could have practiced the claimed methods directed to diagnosing cancer by comparing the expression of Myosin I gene in a test and control sample as claimed without undue experimentation.

Applying the factors enumerated in *In re Wands* demonstrates that claims 51 and 78-95 are enabled and no undue experimentation would be required to make and use the invention directed to methods of diagnosing cancers or for the detection of a propensity towards cancer, comprising the steps of differential detection of myosin I mRNA, myosin I protein, the detection

of differential myosin I mRNA levels, or detection of evidence of differential expression of myosin I.

i. Factors 1 and 2: The nature of the claimed invention and breadth of the claims.

Claims 51 and 78-95 are drawn to methods for diagnosing cancer by determining the differential expression of a myosin I gene products (i.e., protein, mRNA or expression products binding under stringent conditions to a sequence of SEQ ID NO:777).

As taught by the specification, the use of oncogenic retroviruses —whose sequences insert into the genome of the host organism and result in cancer— has allowed the identification of host cancer related sequences such as myosin I, defined as a cancer associated (CA) gene or nucleic acid sequence. See the specification at paragraph 27; paragraph 29, lines 1-2; paragraphs 32 and 287; and Example 1, paragraph 298. In this regard, the specification teaches the use of three mammalian retroviurses (i.e., FeLV, MLV and MMTV) for tagging and identifying protooncogenes. See paragraph 27, last three lines, and paragraph 298. The specification describes that the integration of provirus affects the expression of host genes at or near the site of integration – a phenomenon known as retroviral insertional mutagenesis. See paragraph 49, lines 5-7. Possible changes in the expression of host cell genes due to insertional mutagenesis are taught to include: (i) increased expression of genes near the site of integration, (ii) decreased expression of genes due to functional inactivation caused by the integration, or (iii) expression of a mutated protein that has a different activity to the normal protein. See paragraph 49, lines 7-12.

The specification also teaches that differential expression of the CA genes such as myosin I can be used for diagnosis of cancer or detection of cancer phenotype. See paragraph 161. As will be discussed below, the specification further provides information about various means by which the differential expression of CA genes (including their mRNAs and proteins) can be determined. See Paragraphs 74-133. Thus the present specification shows that the differential expression of myosin I gene which expresses nucleic acid comprising SEQ ID NO:777 can be used as claimed for diagnosis of cancer.

ii. Factors 3 and 4: The relative skill in the art and the state of the prior art.

The Office contends that "[t]he art of cancer diagnosis is unpredictable . . . [that] Tockman (Tockman, M.S. et al. Cancer Research, (SUppl.) 57:2711s-2718s, 1992) teaches that the application of a marker for diagnostic purposes requires a provision of a clear definition of the end point for which the candidate protein or gene is to be a marker; an identification of the relevant clinical specimen in which to detect the marker, and the establishment of a range of marker variability (page 2711s, 2nd column)." Office Action, page 5, paragraph 3.

Applicants submit that the specification complies with the criteria recited in Tockman as follows. As described above, the specification discloses that myosin I gene expressing nucleic acid sequence of SEQ ID NO:777 was discovered through the retroviral insertional mutagenesis as a marker for diagnosis of cancer. The specification teaches that the product of a CA gene such as myosin I can be a marker for cancer diagnosis, when the gene expression is differentially altered in a tissue as compared to a control. See paragraph 161. The end point for which the myosin I is to be a marker is measured, according to the specification, by differential expression that is defined and quantified in terms of up- or down-regulation. See paragraphs 51 and 52. The specification further establishes the range of myosin I gene product variability in terms of, for example, sequence homology (of least 95% to myosin I mRNA) or hybridization at stringent condition (of e.g., 60° C in 5X SSC). See paragraph 65 and 71. The specification further describes means for determining sequence homology in paragraphs 66-69 and provides detail disclosure for hybridization conditions in paragraphs 71-72. The specification also provides information about the biological samples which can be used for detecting the CA gene expression and diagnosing cancer. See paragraph 278. The specification teaches that, for example, laser capture microdissection can be used to obtain samples from tumor and normal tissues. See paragraphs 306 or 316.

The present specification and the state of the prior art at the time the application was filed indicate that the relative skill in the art in relation to the subject matter to which the claimed invention pertains was high. At that time the application was filed, it was routine for a person skilled in the art to use recombinant DNA methods to determine the differential expression of, for example, myosin I gene products comprising SEQ ID NO:777 or a nucleic acid sequence with at

least 95% homology with SEQ ID NO:777 or myosin I protein in tissue samples.

As provided in the specification, it was also routine for one skilled in the art to be able to test myosin I gene or its product for diagnosing cancer. Various means for diction of CA gene's nucleic acid product expression are disclosed in the specification at paragraphs 74 to 92. Various means for diction of CA gene's encoded protein expression are disclosed in the specification at paragraphs 93-133. Thus the specification not only taught that mycosin I gene product can be used to diagnosing cancer; but it also provided detailed support for a skilled artisan to carry out the claimed methods for diagnosing cancer.

iii. Factor 5: The presence of working examples.

The Office contends that "[t]he support for methods of diagnosis amounts to a supposition that detection of myosin I mRNA, or myosin I protein correlates with any and all cancer, or with the specific cancers such as colon cancer, breast cancer or prostate cancer, because there are no working examples demonstrating measurements of myosin I mRNA correlate with any cancers." Office Action, page 5, lines 4-7. Applicants respectfully traverse.

The MPEP, Section 2164.02, states: "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation."

The specification in paragraph 300, provides an example in which the RT-PCR method can be used for analysis of differentially expressed gene. See also Figures 2-4. In paragraph 304, the specification provides an example of detection of elevated levels of cDNAs associated with cancer (e.g., myosin I cDNA) using arrays. Methods for detection of CA sequences (e.g., myosin I gene) in human cancer cells and tissues by way of hybridization are disclosed in Example 5, paragraph 319. Furthermore, generation of antibodies against CA polypeptides (e.g., myosin I polypeptide) is disclosed in Examples 7-8, paragraph 324-326. Various methods for detection of CA proteins (e.g., myosin I protein) have also been disclosed in Examples 9-10, paragraphs 327-328.

The specification also discloses that "[c]omparing expression patterns of uncharacterized genes may provide clues to their function. High throughput analysis of expression of hundreds or thousands of genes can help in (a) identification of complex genetic diseases, (b) analysis of differential gene expression over time, between tissues and disease states, and (c) drug discovery and toxicology studies. Increase or decrease in the levels of expression of certain genes correlate with cancer biology. For example, oncogenes are positive regulators of tumorigenesis, while tumor suppressor genes are negative regulators of tumorigenesis. (Marshall, Cell, 64: 313-326 (1991); Weinberg, Science, 254: 1138-1146 (1991))." See paragraph 8, lines 3-end. The specification also provides means for detection of cancer profile and correlating the expression levels of CA genes (e.g., myosin I) to the cancer phenotype. See paragraphs 161-175.

Therefore, in view of the extensive teachings and exemplifications provided in the specification, a skilled artisan could have reasonably correlated the *in vitro* effects of the claimed methods to their *in vivo* utility in providing means for diagnosing cancers.

iv. Factors 6 and 7: The quantity of experimentation necessary to make or use the invention and the amount of direction or guidance presented in the application.

The person of ordinary skill in the art would be able to practice the claimed invention following the guidance of the specification, using no more than routine experimentation. Myosin I gene and techniques suitable for detecting its differential expression in a test tissue and comparing same to a control were known in the art at the time the application was filed. The specification further provided detail information for a skilled artisan to carry out the claimed method. See the information provided in Example 2 for analysis of quantitative RT-PCR: comparative C_T method; Example 3 for detection of elevated levels of cDNA associated with cancer using arrays; Example 4 for detection of CA-sequences in human cancer cells and tissues; Example 5 for detection of CA sequences in human cancer cells and tissues; Example 6 for expression of cloned polynucleotides in host cells; Example 7 for generation of antibodies against polypeptides; Example 8 for generation of monoclonal antibodies against a CA polypeptide; Example 9 for ELISA assay for detecting CA related antigens; Example 10 for identification and characterization of CA antigen on cancer cell surface; Example 13 for diagnostic imaging using

CA specific antibodies; and Example 14 for immunohistochemical methods disclosed.

Thus, the specification teaches the person of ordinary skill in the art that differential expression of CA genes (including myosin I gene) and their products for diagnosing cancers are important, and that detection of the differential expression leads to diagnosis of cancer. Accordingly, the specification provides ample guidance regarding the structure-function of myosin I gene expression to enable any person skilled in the art to make or use the claimed methods without undue experimentation.

v. Factor 8: The predictability or unpredictability of the art.

The Office further contends that changes in mRNA levels cannot be predictably associated with changes in protein levels. The Office cites Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31., pp. 107-122) with regard to ornithine decarboxylase; McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) with regard to p-glycoprotein; and Fu et al. (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) with regard to p53 protein expression to show that "predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation." Office Action, page 6, lines 11-13. Applicants respectfully traverse.

Applicants submit that none of the references cited by the Office relate to myosin I or cannot be a representative of the relation existing between protein translation and mRNA expression of myosin I. Moreover, even if the Office's assertion that "predictability of protein translation is not necessarily contingent on mRNA expression" were true, the patent statutes do not require absolute predictability, only that it would not require undue experimentation to make and use the claimed invention.

In view of the foregoing arguments, Applicant submit that claims 51 and 78-95 are enabled because, in view of state of art, teachings and exemplifications provided in the application, a person of ordinary skill in the art could make or use the claimed methods without undue experimentation. Accordingly, Applicant respectfully request withdrawal of this rejection.

II. Rejection of claims 78-80 and 82-95 for Enablement

Claims 78-80 and 82-95 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Office acknowledges that the specification is "enabling for methods where the expression product that is detected is an mRNA having a sequence of SEQ ID NO:777." However, the Office alleges that the specification "does not reasonably provide enablement for methods where the expression product that is detected is an mRNA having a sequence at least 98% identical to SEQ ID NO:777, 95% identical to SEQ ID NO:777, or is greater than about 75% in overall homology to SEQ ID NO:777." Office Action, page 7, second paragraph. Applicants respectfully traverse.

Without acquiescing to the reasoning offered in the Action, Applicants have amended claims 78 (from which claim 82 depends) and claim 83 (from which claims 84-87, 89-90 and 93 depend) to include the features of "mRNA comprising SEQ ID NO:777" and "myosin I gene which expresses a nucleic acid comprising SEQ ID NO:777," respectively. Claim 94 (from which claim 95 depends) has also been amended to include the feature of "highly stringent conditions of 50-60° C, 5X SSC, overnight, followed by washing twice at 65° C for 20 minute with each of 2X, 0.5X and 0.2x SSC containing 0.1% SDS." Claims 79-81, 88, 91-92 and 95 have also been canceled without prejudice. In view of the reasoning provided above, claim amendments and cancelations, Applicants submit that this rejection has been rendered moot. Accordingly, Applicant respectfully request that this rejection be withdrawn.

III. Rejection of claims 78-81, 82-92, 94 and 95 for Written Description

Claims 78-81, 82-92, 94 and 95 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office states that "[t]he basis for this rejection is that the specification fails to describe the genus of mRNA expression products of myosin I that have greater than 75% sequence identity to SEQ ID NO:777, or polynucleotide that hybridize under highly stringent conditions to a nucleotide sequence comprising SEQ IDN O:777 [sic], and that are also diagnostic of cancer or diagnostic for a specific cancer." Office Action page 9, lines 11-15. Applicants respectfully traverse.

Without acquiescing to the reasoning offered in the Action, Applicants respectfully submit that this rejection has been rendered moot in view of the above-mentioned claim amendments and cancellations. As such, Applicants respectfully request withdrawal of this rejection.

III. Rejection of claims 83-93 for Written Description

Claims 83-93 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office states that "[t]he claims are drawn to detection of evidence of differential expression, whereas the original claims and the originally filed specification are drawn to measuring actual differential expression. . . . The amended claims are broader in scope than the originally filed claims because detecting evidence of differential expression may include measuring such things as flux through a pathway or measuring genetic mutations." Office Action, page 11, lines 4-9. Applicants respectfully traverse.

Claim 83 (from which claims 84-87, 89-90 and 93 depend) has been amended to recite "detecting evidence of differential expression of myosin I gene which expresses a nucleic acid comprising SEQ ID NO:777," thereby obviating the rejection. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Claims 83-87 and 91-93 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Venter et al. (U.S. Pat. No. 6,821,339; herein after "Venter") allegedly because Venter teaches "SNP sequences and teaches in particular SEQ ID NO:4522, which is identical to instant SEQ ID NO:777. Venter teaches that detection of the provided SNP sequences, of which SEQ ID NO:4522 is one, allows the detection of disease." Office Action, page 12, lines 3-5. Applicants respectfully traverse.

Claim 83 (from which claims 84-87, 89-90 and 93 depend) has been amended to recite "as compared to a control," a feature previously presented in claim 88. As amended, claims 83-87 and 93 do not read on Venter which fails to teach the element of detecting evidence of differential expression as compared to a control. As such, the claims as amended are not anticipated,

reconsideration and withdrawal of the rejection are requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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